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SCIENTIFIC DATA REVIEWS
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Tribufos (DEF®), Addendum to Chronic/Oncogenicity Study in the Rat

TO: Bruce Sidwell PM-53
Reregistration Branch
Special Review and Reregistration Division (H7508C)

1/6/93

FROM: Robert P. Zendzian Ph.D.
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Toxicology Br II
Health Effects Division (H7509C)

THROUGH Karl Baetcke Ph.D.
Chief
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Compound; Tribufos (DEF®) Tox Chem #864 MRID #425536-01

Registration #074801 Registrant; Miles DP barcode; D185169

Action Requested

Review the following document:

Supplemental submission to EPA MRID No. 423351-01, Technical grade Tribufos (DEF®): A Chronic Toxicity/Oncogenicity/Neurotoxicity feeding study in the Fisher 344 Rat. W.R. Christenson, Miles Inc, Study No 88-271-AA, May 1, 1992 (origional report), Sept 30, 1992 (Report Addendum), MRID 425536-01.

Conclusions

In the process of reviewing MRID No. 423351-01 it was discovered that the individual data on the electroretinography of the rats was referenced and assigned a section number but was not included in the submission. Dr. Van Goethem, the Miles toxicologist responsible for the report, was notified of this deficiency by phone during the week of June 22, 1992. This document contains the missing data. Finalization of my review of the basic document was held up until receipt of this document. I have examined this data and conclude that it does not require any change in my evaluation of the basic report. My final review of the basic report has been submitted seperately.

5/18/93

Karl

Attached is the Tribufos document with a recommendation of Special Review. The following is a brief and incomplete history of the chemical.

Tribufos (DEF), and its sulfur analog Merphos, were two of some 40 chemicals listed for RPAR (Rebutable Presumption Against Reregistration) in 1975-6. The two chemicals were considered together because Merphos was activated into DEF, which is the cholinesterase inhibitor, thus they could be expected to have the same toxicity and they were both used only as defoliants on cotton.

In 1979 (memo 4/13/79) I was assigned as pharmacologist for the DEF/Merphos RPAR team and on 7/17/79 completed my neurotoxic review of the chemicals. I identified OP-delayed neurotoxicity, spinal cord lesions and the lack of an antidotal study as possible issues. During the next two years, the issues on these chemicals were debated extensively. The ultimate conclusion was that OP-delayed neurotoxicity was an issue and that there appeared to be no MOS for applicators. However, the studies were not clear on NOELs and there were extensive data gaps. It was recommended that DCIs be sent out to obtain the missing data. No PD-1 was ever written on the compounds. In November 1981 a decision document was written returning DEF/Merphos to registration but it did not include the requirement for the missing studies. This was done dispite strong objections from toxicology.

In 1987 (7/20/87) I wrote a memo to Saunders in registration listing the data requirements for DEF/Merphos and noted that the Agency had taken no action on these chemicals since 1980.

At or shortly before this time California notified the regitrants of these chemicals of the data gaps and required the studies. This started the production of the modern studies on tribufos (DEF) with which I have been intimately involved.

As an apparent result of the California action the registrant cancaled all registrations for Merphos leaving only one cotton defoliant on the market.

Attached is a list of my older memos in my file on this topic. It is grossly incomplete since at that time I had not yet recognized the necessity of keeping everything. Thus the written background on this case by other members of the RPAR group and the PM is probably lost.

RPZ 5/18/93

4/13/1979
Memo Burnam to Zendzian
Merphos (DEF) RPAR review
assignment as pharmacologist for this task

7/17/1979
Memo Zendzian to Ghandi
Neurotoxic Review of DEF and Merphos
Delayed neurtoxicity
spinal cord lesions
antidote

7/28/1980
Memo Chasson to Zendzian
do complete review of DEF/Merphos

7/29/1980
Memo Zendzian to Chasson
reply to above
in 1979 RPAR support team concluded that data do not support
action but did not know how to terminate
new data indicates tox risk? audit Abu-Donia?

8/12/1980
Memo Zendzian to Brown
Toxicology studies needed for DEF and Merphos

8/12/80
Memo Zendzian to Reisa
request for audit Abou-Donia studies on DEF and Merphos
EPA Contract 68-02-2452

8/28/80
Memo Zendzian to Brown
Merphos and DEF, Delayed neurotoxicity and Human exposure
no MOS applicators

10/9/80
Memo Zendzian to Moore
Lab audit Abou-Donia
cannot determine NOELs from methodology
request NOELs for necessary data

10/21/80
Memo Auerbach to Burnum
Audit report from FDA

11/13/1981
Memo Zendzian to Hitch
Decision Docment 11/81
return DEF to registration
does not include recommendation for studies
wash hands of this

7/20/87
memo Zendzian to Saunders
Merphos/DEF data requirements
list of studies required
add special studies
no Agency action since removed from RPAR

Oct 10, 1991
Notice of risk assessment California
regulatory decision in 60 days?
essentially a bibliography
they will write a "Risk Characterization Document

Tribufos

Toxicology Review

Prepared by

5/18/93

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Table of Contents

A. Toxicology Summary

Tribufos (DEF®) is an organophosphate, S,S,S-Tributylphosphorotrithioate, used to defoliate cotton before mechanical harvesting. It is the only pesticide registered in the United States for this use.

Although tribufos is an organophosphate cholinesterase inhibitor in animal species this is probably not its mechanism of action as a cotton defoliant.

Tolerances for tribufos are listed in 40 CFR as follows;

§180.186 Tributylphosphorotrithioate

A tolerance of 0.25 part per million is established for residues of the defoliant tributylphosphorotrithioate in or on cottonseed.

§180.272 S,S,S-Tributyl phosphorotrithioate

Tolerances are established for residues of the defoliant S,S,S-tributyl phosphorotrithioate in or on raw agricultural commodities as follows:

4 parts per million in or on cottonseed.

0.02 part per million (negligible residue) in meat, fat and meat byproducts of cattle goats and sheep.

0.002 part per million (negligible residue) in milk.

§186.5800 S,S,S-Tributyl phosphorotrithioate

A tolerance of 6 parts per million is established for residues of the defoliant tributylphosphorotrithioate in or on cottonseed hulls. Such residue may be present only as a result of application of the defoliant to the growing cotton crop.

No tolerances are listed for cotton seed oil.

The acute toxicity of tribufos is typical of cholinesterase inhibitory chemicals. Signs of toxicity consist of decreased activity, lacrimation, nasal discharge, salivation, diarrhea, tremor and convulsions with death by respiratory arrest. By the Oral and dermal routes technical tribufos is classified in Toxicity Catagory II and by the inhalation route Catagory IV. No data are available on eye irritation. Dermal irritation is mild to moderate, Toxicity Catagory IV. Tribufos is not a dermal sensitizer. Tribufos has been reported in the scientific literature as producing organophosphate type delayed neurotoxicity in the hen following single doses.

The requirements for subchronic oral toxicity studies in the rodent and nonrodent have been waived because acceptable chronic studies are available in the rat and dog.

In a 21 day subchronic dermal toxicity study in the rabbit (0, 2, 11 & 29 mg/kg/day) signs typical of cholinesterase inhibition and deaths occured at the high dose. Dose-related cholinesterase inhibition in plasma, RBC and brain was observed in both sexes at all doses.

In a 90-day subchronic inhalation toxicity study in the rat (0, 0.93, 2.43, 12.2 and 59.5 mg/m^3) cholinesterase inhibition was observed in the blood at 12, and 59.5 mg/m^3 and in the brain at 59.5 mg/m^3. The ERG (a- and b-waves) was depressed at the high dose.

A 90-day neurotoxicity study was performed in the hen by the dermal route (0, 2,6, 11 and 42 mg/kg/day). Clinical signs and histopathology typical of this type of neurotoxicity were observed at the high dose.

In a combined chronic toxicity/oncogeniticy study in the rat (0, 4, 40 and 320 ppm) plasma cholinesterase inhibition was observed at 4 ppm, erythrocyte at 40 ppm and brain at 320 ppm. At 320 ppm retinal atropy (degeneration) was observed in all animals at 12 months while at 24 months ocular damage included cataract, lens opacity, corneal opacity corneal neovascularization and retinal atropy. Additional high dose toxicity included autolysis and vacular degeneration of the small intestine and vacular degeneration of the adrenals both first observed at 12 months.

A chronic dog study (0, 4, 16, and 64 ppm) showed plasma cholinesterase inhibition at 16 ppm and erythrocyte inhibition at 64 ppm. No other toxic effects were observed.

A mouse oncogenicity study (0, 10, 50 and 250 ppm) showed dose related cholinesterase inhibition at all doses. At 50 ppm histopathology showed damage to the adrenals and small intestine. Increased mortality was observed at 250 ppm with a statistically significant incidence of liver hemangiosarcoma, small intestine adrenocarcinoma and bronciolar adenoma.

The rat combined chronic toxicity/oncogenicity study showed no increase incidence of tumors.

A quantitative risk assessment was performed based on the mouse study and the following Q_1*s calculated;

Male	Liver Hemangiosarcoma	1.136×10^{-1}
	Small Intestine Adenocarcinoma	0.479×10^{-1}
	Combined	2.227×10^{-1}
Female	Alveolar/Bronchiolar Adenoma	1.190×10^{-1}

Teratogenicity studies in the rat (0, 1, 7 and 28 mg/kg/day) and rabbit (0, 1, 3 and 9 mg/kg/day) were negative. Toxicity

was observed in the dams but no fetal toxicity was observed at the highest doses tested.

In a 3-generation reproduction study in the rat (0, 4, 32 and 260 ppm) dose related cholinesterase inhibition was observed at all doses. The only treatment related effect on reproduction was a significant incerease in dead pups in the F1a and F2a litters at 260 ppm.

All mutagenicity tests were negative.

In a metabolism study tribufos was rapidly absorbed, extensively and completely metabolised and the metabolic products rapidly excreted.

A dermal absorption study of tribufos in the rat showed significant skin residue at 1, 4 and 10 hours post dose which was absorbed at 168 hours post dose. Maximum absorption was 34-44% after the 168 hour exposure.

The only remaining data gap is a primary eye irritation study (81-4).

Three toxicological issues have been identified; organophosphate type delayed neurotoxicity, eye toxicity and oncogenicity.

In a 90-day dermal study in the hen delayed neurotoxicity was observed at 42 mg/kg/day with a NOEL of 11 mg/kg/day.

In a 90-day subchronic inhalation toxicity study in the rat the ERG (a- and b-waves) was depressed at the high dose (59.5 mg/m^3) indicative of a toxic effect on the retina. In a chronic toxicity study in the rat complete retinal atropy was observed at 12 months at the high dose (320 ppm). At 24 months ocular damage included cataract, lens opacity, corneal opacity corneal neovascularization and retinal atropy. Expressed in mg/kg/day the high doses in these two studies were essentially the same (22 mg/kg/day and 16.8-21.1 mg/kg/day respectively).

A mouse oncogenicity study showed a statistically significant incidence of liver hemangiosarcoma, small intestine adrenocarcinoma and bronciolar adenoma. The rat oncogenicity study showed no increase in tumors. Based on the mouse study, the HED Peer Review Committee classified tribufos as a Class C carcinogen and recommended low dose extrapolation by calculation of a Q_1*.

The combination of three serious toxic efects in a single chemical is considered sufficient to recommend Special Review of tribufos.

B. Toxicology Profile

81 Series Acute toxicity and Irritation Studies

81-1 Acute Oral

Sufficient data are available on the acute oral toxicity of tribufos in rats. Doses tested and mortality: Males 294 (0/5/), 429 (3/5) and 555 (5/5) mg/kg; females 192 (0/5). 235 (4/5) and 294 (4/5) mg/kg. LD_{50} both sexes between 192 and 235 mg/kg. Signs of toxicity at all doses (decreased activity, lacrimation, nasal discharge, salivation, diarrhea, tremor, convulsions. Deaths occured within 7 days after dosing. Toxicity Catagory II. MRID 419549-03

81-2 Acute Dermal

Sufficient data are available on the acute dermal toxicity of tribufos in the rabbit. Doses tested and mortality: Males 500 (0/5), 1000 (2/5) and 2000 (5/5)mg/kg; Females 500 (0/5), 1000 (2/5) and 2000 (5/5) mg/kg. LD_{50} > 1000 and < 2000 mg/kg. Toxic signs observed at all doses consisting of muscle fasciculations, decreased activity, perianal stain, clear nasal discharge. Toxicity Catagory II. MRID 419549-02

81-3 Acute Inhalation

Sufficant data are available on the acute inhalation toxicity of tribufos in the rat. Doses tested in a four hour exposure were; males 2920, 5690 and 6030 mg/m^3; females 1590, 2920 and 3190 mg/m^3. Signs indicative of cholinesterase inhibition were observed at all doses. The LC_{50} for males was 4650 (1410-6180) mg/m^3 and for females 2460 mg/m^3. Toxicity Catagory III. MRID 417823-01

81-4 Primary Eye Irritation

No data are available on the primary eye irritation properities of tribufos. A study is required.

81-5 Primary Dermal Irritation

Sufficient data are available on the primary dermal irritation properities of tribufos in the rabbit. A single dermal dose of 0.5 ml of the neat material was applied and protected by an occlusive patch for four hours. Mild to moderate erythrema, dry cracked skin and edema were observed (primary irritation score 3.7). Toxicity Catagory IV. MRID 418962-03

81-6 Dermal Sensitization

Sufficient data are available on the primary dermal sensitization properities of tribufos in the guinea pig. Tribufos was not a sensitizer when tested with the Buehler Topical Closed-Patch test. MRID 416188-12.

81-7 Acute Delayed Neurotoxicity

No data are available on the acute neurotoxic effects of tribufos. Literature references and an acceptable 90-day dermal study show that tribufos produces organophosphate type delayed neurotoxicity. An acute study is not required.

82 Series Subchronic Testing

82-1 Subchronic Oral

No data are available on the subchronic oral toxicity of tribufos. Studies are not required in the rodent and nonrodent species because acceptable chronic studies are available in the rat and dog.

82-2 Subchronic Dermal (21-day)

Sufficient data are available on the subchronic dermal toxicity of tribufos in the rabbit. Doses tested, 0, 2, 10 & 25 mg/kg/day nominal (0, 2, 11 & 29 mg/kg/day actual). At 29 mg/kg/day 1 male and 4 females died or were sacrificed in extremis. Signs of dose-related toxicity were observed in both sexes at 11 and 29 mg/kg/day, with a greater effect at the higher dose. Mild to moderate dermal irritation was observed at 11 & 29 mg/kg/day in both sexes. At termination, dose-related depression of cholinesterase activity was observed in all doses in both sexes in plasma, erythrocyte and brain. Statistically significant depression ($p<0.05$) was observed in plasma (males) and erythrocytes (females) at 2 mg/kg/day and in all parameters in both sexes at 11 & 29 mg/kg/day. No recovery was observed in erythrocyte and brain activity at 33-34 days (14 days post dose). MRID 420072-01

82-3 Subchronic Dermal (90-day)

No data are available on the 90-day subchronic dermal toxicity of tribufos. Based on the use pattern, a study is not required.

82-4 Subchronic Inhalation

Sufficient data are available on the subchronic inhalation toxicity of tribufos. Doses administered were 0, 1, 2, 12 & 60 mg/m^3 nominal (0, 0.93, 2.43, 12.2 & 59.5 mg/m^3 actual).

Cholinesterase inhabition in the RBC at 12 & 60 mg/m^3 in both sexes, in the plasma at 12 & 60 mg/m^3 in males, at 60 mg/m^3 in females, and in the brain at 60 mg/m^3 both sexes. The ERG was depressed (a- and b- waves) at 60 mg/m^3 in both sexes. The adrenals showed cortical fat deposition at 60 mg/m^3 in both sexes. MRID 423998-01

82-5 Subchronic Neurotoxicity

Sufficient data are available on the subchronic neurotoxicity of tribufos by the dermal route. A 90-day dermal neurotoxicity study was performed in hens. Doses tested were 0, 2.6, 11 and 42 mg/kg/day. Triothrocresolphosphate (TOCP) was utilized as a positive control at 18 mg/kg/day. Doses were applied to the comb. Effects observed in the tribufos treated hens were failure to gain weight (LOEL 11 mg/kg/day, NOEL 2.6 mg/kg/day), ataxia in seven of twelve hens (LOEL 42 mg/kg/day, NOEL 11 mg/kg/day) and whole blood cholinesterase inhibition (LOEL 2.6 mg/kg/day [LDT]). Histopathology indicative of neurotoxicity was observed primaraly in the brain and spinal cord (LOEL 42 mg/kg/day, NOEL 11 mg/kg/day). MRID 420072-02

83 Series Chronic and Long Term Studies

83-1 Chronic Toxicity

Sufficient data are available on the chronic toxicity of tribufos in the rat and the dog. Results of the rat study are presented below under Sec 83-5 Combined Chronic Toxicity/ Oncogenicity Studies.

A chronic study was performed in the dog at doses of 0, 4, 16 & 64 ppm. Inhibition of plasma cholinesterase was observed in both sexes (LOEL 16 ppm NOEL 4 ppm) as was inhibition of erythrocyte cholinesterase in both sexes (LOEL 64 ppm NOEL 16 ppm), a possible decrease in number of erythrocytes at 64 ppm was observed in both sexes. No other toxic effects were observed. MRID 420072-03

83-2 Oncogenicity

Sufficient data are available on the oncogenic potential of tribufos with studies in the mouse and the rat. Results of the rat study are presented below under Sec 83-5 Combined Chronic Toxicity/Oncogenicity Studies.

In the mouse oncogenicity study, mice were dosed at 0, 10, 50 or 250 pmm for 90 weeks. At 10 ppm, decreased plasma and RBC cholinesterase was observed in both sexes and decreased brain cholinesterase in males. At 78 weeks males showed decreased MCV and MCH and at week 90 females showed decreased

hematocrite. At 50 ppm, an increased number number of males showed paleness and hunched backs. At 78 weeks males showed decreased MCV and MCH and at week 90 decreased MCH. At week 90 females showed decreased RBC count, hemoglobin and hematocrite. Histopathology of the males showed; adrenals amyloid, epididymis hyperspermatogenensis, small intestine amyloid and vacuolar degeneration epithelium, spleen hematopoiesis. At 250 ppm loose stools were observed in females, enlarged abdomen in both sexes, increased mortality/decreased life span in both sexes and increased food consumption and body weight in both sexes. Decreased RCB count, hemoglobin, hematocrite, MCV and MCH was observed in males and decreased RCB count, hemoglobin and hematocrite in females. Histopathology in males showed; adrenals degeneration, liver hemangiosarcoma*, rectum acute inflammation, necrosis and ulcer, small intestine adenocarcinoma*, dilated/ distended and mucosal hyperplasis. In females histopathology showed; adrenals calcification and degeneration/ pigmentation, caecum edema, liver hypertropy, lung alveolar/ bronchiolar adenoma*, mesenteric lymph node congestion, rectum acute inflamation, necrosis and ulcer, small intestine adenocarcinoma*, dilated/distended, mucosal hyperplasia. (* statistically significant increase in tumors) MRID 411710-01.

83-3 Teratogenicity

Sufficient data are available on the teteratogenic potential of tribufos in the rat and the rabbit.

In the rat teratology study, pregnent rats were dosed orally at 0, 1, 7 and 28 mg/kg/day (days 6-16). Maternal RBC and plasma cholinesterase activity was depressed at 7 and 28 mg/kg/day and brain activity at 28 mg/kg/day. Maternal weight gain was decreased at 28 mg/kg/day. Maternal toxicity LEL 7 mg/kg/day, NOEL 1 mg/kg/day. Fetotoxic NOEL 28 mg/kg/day (HDT). Tribufos was not teratogenic in this study. MRID 401906-01

In the rabbit teratology study, pregnent rabbits were dosed at 0, 1, 3 or 9 mg/kg/day, (days 7-19). Plasma and RBC cholinesterase activity were significantly reduced at all doses on day 20 and RBC at all doses on day 28. Does failed to gain weight at 9 mg/kg/day during dosing. Maternal toxicity LEL 9 mg/kg/day, NOEL 3 mg/kg/day. Fetal toxicity NOEL 9 mg/kg/day (HDT). Tribufos was not teratogenic in this study. MRID 401906-02

83-4 Reproduction

Sufficient data are available on the reproductive toxicity of tribufos from a 2 generation study in the rat.

In a 2-generation reproduction study rats were dosed at 0, 4, 32 and 260 ppm. The only compound-related effect on reproduction was a significant increase in dead pups in the F1a and F2a litters (LOEL 260 ppm, NOEL 32 ppm). The most sensitive effect was blood cholinesterase inhibition in adults. The LOEL for plasma and erythrocyte cholinesterase depression was 4 ppm (LDT). No NOEL was determined. In pups, decreased cholinesterase activity was greatest at 21 days in the F1a females and plasma cholinesterase activity significantly decreased (LOEL 32 ppm, NOEL 4 ppm). MRID 420401-01

83-5 Combined Chronic Toxicity/Oncogenicity Studies

A rat study is available that satisfies the requirement for a combined chronic toxicity/oncogenicity study (MRID 423351-01).

In a combined chronic toxicity/oncogenicity study in the the rat doses were 0, 4, 40 and 320 ppm. (males 0.0, 0.2, 1.8 and 16.8 and females 0.0 0.2, 2.3 and 21.1 mg/kg/day) No oncogenic response was observed. Because of the variety of nononcogenic compound related effects observed they are listed in order below at the lowest dose at which they were observed: (Males, Females
12 months)

4ppm
decreased plasma cholinesterase M&F
40ppm
decreased weight gain M
decreased RBC count, Hemoglobin, hematocrite. M&F
decreased cholosterol, calcium M
decreased RBC cholinesterase M&F
320ppm
decreased weight gain F
increased food consumption M&F
terminal opthamological exam; cataract, lens opacity, corneal opacity, corneal neovascularization, iritis/uveitis M&F
terminal EKG; unrecordable M&F
decreased Totprotein, globulin, cholesterol, calcium M&F
increased BUN M&F
decreased brain cholinesterase M&F
Adrenals; vacular degeneration 12m M&F
Eyes; retinal atropy 12m M&F
Small intestine; autolysis, vacoular degeneration 12m M&F
Eyes; retinal atropy, uveitis, cataract, neovascularization 24m M&F
Optic nerves; atropy 24m M&F
Small intestine; autolysis, vacoular degeneration, hyperplasia 24m M&F
MRID 423351-01

84 Series Mutagenicity

84-2 Mutagenicity Tests.

Sufficient data are available on the mutagenic potential of tribufos. Tribufos was negative in all tests.

A mutagenicity study was performed in salmonella. Tester systems used were the Salmonella typhimurium histidine auxotrops TA98, TA1000, TA1537 and TA1538 as described by Ames et al (1975). The test compound was negative without and with microsomal activation at concentrations up to 10,000 ug/plate. MRID 414591-01

A study of unscheduled DNA systhysis was preformed on rat primary hepatocytes. The test compound was negative at concentrations of 0.0001 to 0.006 ul/ml. Higher concentrations were toxic. MRID 414591-02

A test for chromosomal aberrations was performed in chinese hamster ovary cells. The test compound was negative without and with microsomal activation. Doses tested without activation, 0.004, 0.007, 0.013, 0.025 and 0.05 ul/ml, showed toxicity at 0.025 and 0.05 ul/ml. Doses tested with activation, 0.007, 0.013, 0.025, 0.05 and 0.1 ul/ml, showed toxicity at 0.05 and 0.1 ul/ml. MRID 414591-03

85 Series Special Studies

85-1 Metabolism

Sufficient data are available on the metabolism of tribufos in the rat.

In the metabolism study of [1-^{14}C] Tribufos was performed in 5 male and 5 female rats single oral dose, 5mg/kg or 100 mg/kg or 5 mg/kg/day X 14 days cold tribufos followed by 5 mg/kg [1-^{14}C] Tribufos. 55 to 80 % was absorbed of which 90+% was excreted in 72 hours. There was no significant tissue residue. Absorbed material was extensively and completely metabolized. MRID 420345-01

85-3 Dermal Absorption

Sufficient data are available on the dermal absorption of tirbufos.

A dermal absorption was performed in the rat at doses of 2.8, 14.0 & 140 ug/cm^2 and exposures of 1, 4 & 10 hours plus a 10 hour wash with 168 hr exposure. Significant skin residue remained after the soap and water wash at 1, 4, & 10 hours (30-40%). the 10 hour residue was mostly absorbed at 168 hrs. Maximum absorption was 34-44 % after the 168 hour exposure. MRID 423500-03

C. Data Gaps

Tributos is registered for food crop uses. Therefore the following Guideline toxicology studies are required for registration.

81-1 Acute Oral
81-2 Acute Dermal

81-3 Acute Inhalation
81-4 Primary Eye Irritation
81-5 Primary Dermal Irritation
81-6 Dermal Sensitization
81-7 Acute Delayed Neurotoxicity

82-1 Subchronic Oral, two species rodent and nonrodent
82-2 Subchronic Dermal (21-day)
82-4 Subchronic Inhalation
82-5 Subchronic Neurotoxicity (if positive in 81-7 Acute Delayed Neurotoxicity)

83-1 Chronic Toxicity, two species rodent and nonrodent
83-2 Oncogenicity, two species
83-3 Teratogenicity, two species
83-4 Reproduction
84-2 Mutagenicity Tests.

85-1 Metabolism

Based on this assesment of the toxicology data base the following Guideline toxicology study has been identified as a data gap and is required.

81-4 Primary Eye Irritation

D. Toxicological Issues

1. Organophosphate type delayed neurotoxicity

Neurotoxicity is broadly defined as any effect on the nervous system. The effect may be reversible or irreversible and may be caused by single or repeated dosing. A particularly dangerous neurotoxicity was demonstrated in man during prohibition. A concoction called Jamaica Ginger was contaminated with tri-o-cresyl phosphate (TOCP), a component of the organic solvent used to prepare ginger extract. Victims developed a paralysis of the legs and arms whose severity varied with exposure. Animal studies identified TOCP as the toxic agent and characterized a syndrome which has been called Organophosphate Type Delayed Neurotoxicity. Subsequently this syndrome was observed following accidental human exposure to the pesticide leptophos and the experimental compound mipafox, both organophosphate inhibitors of cholinesterase.

Organophosphate type delayed neurotoxicity is characterized as follows: A delay in the order of 10-14 days between a single effective dose and the appearance of clinical and histopathological signs. The appearance of the delayed effect well after recovery from the acute toxicity of the compound. No apparent relationship between the compound's ability to inhibit blood cholinesterases and its ability to produce the delayed effect. The appearances of abnormalities of gait which may proceed to complete paralysis and are generally irreversible. The destruction of nerve axons in the sciatic nerve and in the spinal cord and the subsequent disappearance of the myelin sheath which surrounded the lost axons. The delayed toxic effect can also be produced by daily administration of doses which individually will not produce the acute toxic response, i.e., the delayed toxicity is cumulative.

Animal studies with TOCP showed that the toxic syndrome could not be produced in rats and mice and was produced only with inconsistent or atypical results in dogs and cats. The syndrome has been demonstrated in bovine and primate species. The chicken has been shown to consistently demonstrate the syndrome with the three compounds that are active in man and is the species of choice in modern screening tests for this type of toxicity.

Reports that tribufos produced this type of toxicity in the chicken were published by Casida et al in 1963, Baron and Johnson in 1964 and Gaines in 1969. Gaines reported the results of a single dose toxicity study with tribufos in the hen. A single oral dose of 200 mg/kg was administered and the hens observed for the onset of "leg weakness". The onset of leg weakness was delayed 14 to 28 days following administration

of tribufos and was still apparent 30 days after treatment. Gaines commented that "This is somewhat typical of the reaction of chickens to treatment with triorthrocresylphosphate, the classical compound studied for this effect."

In an agency sponsored study, Abou-Donia determined that tribufos produced organophosphate type delayed neurotoxicity in hens after a single oral dose and with 90-day oral administration. Abou-Donia and coworkers subsiquently reported on the effects of route and number of doses on tribufos neurotoxicity (1979a&b).

Single oral doses of 100, 200, 300, 400, 500, 600 and 700 mg/kg produced dose related ataxia indicative of OP delayed neurotoxicity. However, deaths were reported at doses of 400 and up, all hens died at 800, 900 and 1000 mg/kg. Single dermal doses of 400 and 1000 mg/kg produced dose related ataxia and histopathological evidence in the spinal cord at 1000 mg/kg.

Repeated daily doses of 2.5, 5, 10, 20, 40 and 80 mg/kg/day produced dose related increases of ataxia at shorter durations of dosing with increasing dose. Deaths occured at 20, 40 and 80 mg/kg/day and survival time decreased, respective mean survival time, 32, 16 and 16 days. Histopathology was observed only in the spinal cord of 3/5 hens at 80 mg/kg/day. No effects were observed at doses of 0.5 and 1.0 mg/kg/day for 90 days. Dermal doses of 20 and 40 mg/kg/day for 90 days produced dose related ataxia, the time to effect decreaed and the severity of effect increased with increasing dose.

Based on these reports and because the major route of tribufos exposure was by the dermal route, the Agency requested a 90-day dermal neurotoxicity study in the hen to determine LEOL and NOEL doses (MRID 420072-02). The doses tested were 0, 2.6, 11, & 42 mg/kg/day tribufos and 18 mg/kg/day TOCP (the positive control).

The first sign of toxicity, failure to grow when compared with controls was observed in the 11 mg/kg/day hens at approximately day 14. However, significant ($p \leq 0.05$) weight depression was only observed in the 42 mg/kg/day at day 35 and thereafter and in the positive control group (TOCP 18 mg/kg/day) at day 28 and thereafter.

The first sign of neurotoxicity, ataxia, was observed in 7/12 hens at 42 mg/kg/day starting on day 42 (LOEL 42 mg/kg/day, NOEL 11 mg/kg/day). Signs increased in severity for the duration of the study but were never sufficient to require premature sacrifice.

Significant ($p \leq 0.05$) whole blood cholinesterase depression was observed at all doses in the treated animals from day 4

to termination (NOEL < 2.6 mg/kg/day). In contrast, significant whole blood cholinesterase depression was only observed in the TOCP hens on days 4 and 25 which is indicative of its relatively weak anticholinesterase activity.

Histopathological observations of the brain, spinal cord and fibular, tibular and sciatic nerves are presented in Table A. As noted in the heading for the table, grade scores of abnormalities have been converted into numerical scores. The lesion of OP delayed neurotoxicity is a Wallarian degeneration of the axon followed by a degeneration of the mylin. This degeneration is accompnied by local 'digestion' from release of cell bound enzymes followed by macrophage accululation to scavage the remaining cellular residue. For each tissue examined, pathology is assesed under the following observed conditions; Degeneration, axonal; demylination; digestive chamber; macrophage accumulation and infiltrate, lymphatic. For this pathology no increase in lymphatic infiltration was observed.

The pathology is clearly shown by the response of the Group E hens to TOCP, the positive control. The primary lesion is in the spinal cord, which is imposed on a low level of background lesions as shown in the negative control. This is followed by lesions in the brain and the sciatic nerve and its branches. Toxicity is clearly established at 42 mg/kg/day of tribufos (DEF). However, there is little if any evidence of pathology in the nerves examined. This is typical of the progression of the pathology. The final page of Table A summarizes the mean scores for brain and spinal cord showing a clear response at 42 mg/kg/day tribufos and 18 mg/kg/day for the positive control TOCP.

A dermal LOEL for OP type delayed neurotoxicity of 42 mg/kg/day and a NOEL of 11 mg/kg/day for tribufos is clearly extablished.

2. Eye toxicity

In Japan organophosphate pesticides have been observed to produce toxic effects on the eye. Extensive human poisoning produced a syndrome of effects on vision ranging in severity from myopia to congestion or atropy of the optic nerve. Although the reports mentioned exposure to several organophosphates, the information did not permit identifying a particular compound as bioactive. Experimental studies with the organophosphate fenthion on rats demonstrated a syndrome of toxic effects on the eye beginning with functional abnormalities in electrical activity and columinating in retinal degeneration following chronic dosing.

In 1984 OPP received reports of chronic studies of methyl and ethyl parathion in rats that showed toxicity to the eyes

at a dose of 50 ppm. Retinal degeneration was detected by direct observation in females at the high dose and light microscophy detected additional lesions at the same dose in females. A second ethyl parathion study, received in 1987, confirmed and extended these effects at a dose of 32 ppm. Terminal observations on the eyes indicated decreased ERG (LEL 8 ppm, NOEL 2 ppm), gross retinal abnormalities, histopathology indicative of blindness and possible increase in cataracts (LEL 32 ppm, NOEL 8 ppm) in the females.

In 1985 OPP acted on the parathion reports by requiring special eye studies on these compounds and other organophosphates in the reregistration process.

In 1990 OPP received a (6)(2)(2) notification of a feeding study of tribufos (DEF) in rats which showed complete distruction of the visual layer of the retina at a dose of 320 ppm after 12 months of dosing.

The final report of this study was received in 1992 (MRID 423191-01). The doses tested were 0, 4, 40 and 320 ppm in the diet. At 12 months treatment related effects were observed in the eyes. Ocular effects consisted of retinal atropy in all high dose males and females. Effects on the retina were also observed at the 24 month sacrifice. The unique character of this pathology was described by the pathologist as follows;

"Retinal atrophy, in the 320 ppm groups, was characterized microscopically by diffuse loss (disappearance) of most of the outer layers of the retina, including the layer of rods and cones, outer limiting membrane (assumed), the outer nuclear layer, the outer plexiform layer, and sometimes portions of the inner nuclear layer. The pigment epithelium, considered anatomically to be the outermost retinal layer, was present, but contained increased eosinophilic granular to flocculent cytoplasmic material which was of sufficient quantity to distort the cell in some instances. The coroid was reduced in thickness in approximate relation to the thickness of the remaining retina; it appeared functional in terms of patency of vessels and the presence of blood. The layer of optic nerve fibers and the ganglion cell layer were sometines reduced in thickness, but this was variable in occurence."

"In the typical presentation at either one or two years, the appearance was of diffuse loss of the rods and cones, outer limiting membrane, outer nuclear layer and outer plexiform layer, with "collapse" of the remaining inner layers onto the pigment epithelium. Occasional darkstaining nuclei, remnents of the outer nuclear layer, could be noted at the edge of the remaining inner nuclear layer. In the extreme presentation,

the inner nuclear layer was also affected, with gaps in the layer and distortions of the normal layered appearance (i.e., it demonstrated a dysplastic appearance) and more thinning of the layer than in the control or less affected animals."

"The retinal changes in the 320 ppm animals were essentially confined to that group by virtue of being diffuse and bilateral, and by some evidence that the lesion started in the central portion of the retina. In several 320 ppm rats which died prior to one year on study, but later than three months on study, early outer segmental degeneration could be detected in the central portions of the retina. There was no change apparent in the 320 ppm animals which died [immediately] following the three month bleeding interval."

"The frequency of diffuse, bilateral retinal atrophy at one year was: (M-0/20, 0/10, 0/10, 19/20*; F-0/20, 0/10, 0/10, 20/20*); in two year rats: (M-1/50, 0/50, 0/50, 50/50*; F-0/50, 2/50, 0/50, 40/50*)." [*$p \leq 0.05$]

"Retinal atrophy in other groups, including the control, was clearly differentated from the lesion in the 320 ppm groups in several ways:

1. Most occurances of atrophy at two years were peripheral in distribution; there were several instances at one year also. This change is characterized by thining of the portion of the retina near the ciliary body, and is considered an aging change: a one year (M-1/20, 0/10, 1/10, 0/20; F-1/20, 1/10, 0/10, 0/20); at two years: (M-11/50, 15/50, 21/50, 0/50*; F-30/50, 33/50, 36/50, 0/50*)." [*$p \leq 0.05$]

2) Most occurances were unilateral atrophy, which was usually related to an inflamatory change or other lesions: at one year (M-4/20, 1/10, 3/10, 1/20; F-4/20, 3/10, 1/10, 0/20); at two years: (M-11/50, 15/50, 18/50, 0/50*; F-21/50, 24/50, 18/50, 0/50*). The peripheral lesions taken as a group tended to be unilateral as well: all at one year and at two years (M-6/50, 9/50, 13/50, 0/50*; F-17/50, 19/50, 15/50, 0/50*). There was no bilateral retinal atrophy in control, 4, or 40 ppm groups at one year; there was a small proportion in those groups at two years (M-5/50, 6/50, 8/50, 50/50*; F-13/50, 16/50, 21/50, 41/50*)." [*$p \leq 0.05$]

3) Electroretinography showed essenially complete loss of retinal response on stimulation in the 320 ppm group and normal responses in the other treated groups. This confirmed the microscopic impressions of compound effect in the 320 ppm groups only."

In 1992 a 90-day inhalation study of tribufos in the rat was received (MRID 423998-01). Doses tested were 0, 1, 2, 12 & 60 mg/m^3 nominal (0, 0.93, 2.43, 12.2 & 59.5 actual). Cholinesterase inhabition was observed in the erythrocytes at 12 & 60 mg/m^3 in both sexes, in the plasma at 12 & 60 mg/m^3 in males and at 60 mg/m^3 in females and in the brain at 60 mg/m^3 in both sexes. Terminal electroretinograms (ERG) showed depressed a- and b- waves at 60 mg/m^3 in both sexes. No observational or histopathological alterations were observed in the eyes.

In the rat chronic/oncogenicity study discussed above the compound produced a retinal toxicity characterized histologically by complete loss of the sensery layer in all rats of both sexes after a minimum of 12 months of treatment at a dose level of 320 ppm.. The sensery cells (rods and cones) of the retina are the source of the a- wave of the electroretinogram (ERG). In this study depression of the a-wave was observed at the high dose (60 mg/m^3). The doses of the two studies are presented below and converted into mg/kg/day.

Inhalation study		Chronic/onco study		
mg/m^3	mg/kg/day	ppm	mg/kg/day	
			males	females
0.0	0.0	0	0.0	0.0
1.0	0.3	4	0.2	0.2
2.0	0.9	40	1.8	2.3
12.0	4.5	-	-	-
60.0	22.0	320	16.8	21.1

The high dose in each study produced essentially the same mg/kg/day dose and as such the effect on the ERG in this inhalation study can be considered predictive of the retinal damage observed in the chronic/ocogenicity study.

3. Oncogenicity

On February 3, 1989 the Registrant sent a 6(a)(2) letter to the Agency on the results of a mouse oncogenicity study with tribufos. Statistically significant incidences of adenocarcinoma/carcinoma in the small intestine in both sexes, hemangiosarcoma in the liver of the males and alveolar/ brochiolar adenoma in the lungs of the females, all at the high dose, were observed. The report of the study was submitted to the Agency in July 1989 and was fowarded to HED for review in December 1989. An HED peer review of tribufos was held on June 13, 1990 to consider the results of the mouse study. "The committee concluded that Tribufos should be classified as a

Group C Possible Human Carcinogen, and recommended that a low dose extrapolation model be applied to the experimental animal tumor data be used for quantification of human risk (Q_1†)." This was an interim classification pending the receipt of an acceptable rat study. An acceptable rat oncogneicity study has been received and is negative for tumor production. This data will not change the June 13th classification.

Rat Studies

A combined chronic/oncogenicity study in the rat showed no increase in the incidence of tumors at any dose in either sex. MRID 423351-01. A detailed presentation of the results of this study is to be found in section 2 under 'Eye Toxicity'.

Mouse studies

A 90 week oncogenicity study in the Crl:CD-1(ICR)BR strain mouse was performed at doses of 0, 10, 50 and 250 ppm in the diet. At the high dose, this study showed an incidence of adenocarcinoma/carcinoma in the small intestine in both sexes which was statistically significant in the females. hemangiosarcoma in the liver of the males and alveolar/ brochiolar adenoma in the lungs of the females (MRID 411710-01).

Compound related effects were observed at all doses in both sexes. Effects are presented by dose below at the lowest dose at which they were observed.

Nominal dose of 10 ppm

Statistically significant decreases in plasma cholineterase activity at weeks 53, 78 and 90 all doses in both sexes.

Statistically significant decreases in RBC cholineterase activity at weeks 78 and 90 all doses in both sexes.

Statistically significant decreases in brain cholinesterase activity at week 93 (termination) all doses in males.

At week 78 in the males, a significant decrease in mean cell volume and mean cell hemoglobin was observed at 10 and 50 ppm and significant decreases in red cell count, hemoglobin, hematocrit, mean cell volume and mean cell hemoglobin at 250 ppm. At week 90 in the males, a significant decrease in mean cell hemoglobin was observed at 50 ppm and significant decreases in red cell count, hemoglobin, hematocrit, mean cell volume and mean cell hemoglobin at 250 ppm. At week 90 in the females, a significant decrease in hematocrite was observed at 10 ppm and significant decreases in red cell count, hemoglobin and hematocrit at 50 and 250 ppm.

Nominal dose of 50 ppm

Statistically significant increased number of males showing paleness and hunched back.

Table 1. Statistically significant histopathological observations, at 50 ppm, from the incidence table.

	MALES Dose (ppm)				FEMALES Dose (ppm)			
Organ & Disease	Cont	10	50	250	Cont	10	50	250
Adrenals	50	50	50	50	50	50	50	49
Amyloid	5/50 3.8	6/50 3.3	15/50* 3.5	9/50 3.1	4/50 2.5	7/50 2.4	3/50 2.7	3/49 2.7
Epididymis	50	50	50	50				
Hyperspermatogenesis, NOS	2/50 2.0	6/50 2,2	10/50* 2.1	3/50 2.0				
Small Intestine	50	50	50	50	50	50	50	50
Amyloid, NOS	6/50 2.7	7/50 2.6	20/50* 2.8	9/50 2.4	6/50 2.7	9/50 2.9	10/50 2.9	8/50 2.4
Degeneration, Vacuolar Epithelium	0/50	1/50 2.0	8/50* 2.1	28/50* 2.5	0/50	0/50	11/50* 1.7	28/50* 2.6
Spleen	50	50	50	50	50	50	49	50
Hematopoiesis, NOS	6/50 2.0	6/50 2.7	14/50* 2.8	19/50* 2.5	16/50 2.6	14/50 2.4	18/50 2.7	20/50 2.2

observed/# examined; mean of severity codes(1-5); B = Benign; M = Malignant; NOS = Not Otherwise Specified; *P≤0.05

Nominal dose of 250 ppm

Statistically significant increased number of females showing loose stool and enlarged abdomen and males showing enlarged abdomen.

Increased mortality, between 72 and 90 weeks, and a concurrent decrease in life span in both sexes.

Increased mean food consumption and body weight in both sexes during the latter portion of the study.

Table 2. Statistically significant histopathological observations at 250 ppm from the incidence table. Note particularly the increased incidence of tumors in the liver, lung and small intestine.

	MALES Dose (ppm)				FEMALES Dose (ppm)			
Organ & Disease	Cont	10	50	250	Cont	10	50	250
Adrenals	50	50	50	50	50	50	50	49
Calcification	0/50	0/50	0/50	4/50 1.0	0/50	2/50 1.5	0/50	5/49* 1.4
Degeneration/ pigmentation, NOS	17/50 1.4	15/50 1.6	21/50 2.0	39/50* 2.6	18/50 2.2	26/50 2.5	22/50 2.3	38/49* 2.7
Degeneration, NOS	0/50	0/50	1/50 1.0	22/50* 2.4	2/50 2.0	0/50	1/50 2.0	3/49 2.0
Caecum	50	50	50	50	50	50	50	50
Edema, NOS	4/50 2.0	6/50 2.0	5/50 2.4	10/50 2.1	6/50 2.0	3/50 2.0	4/50 1.8	17/50* 2.1
Liver	50	50	50	50	50	50	50	50
Hemangiosarcoma	1/50 M	1/50 M	4/50 M	7/50* M	2/50 M	2/50 M	2/50 M	1/50 M
Hypertropy, NOS	1/50 2.0	0/50	1/50 2.0	4/50 1.5	0/50	2/50 2.0	0/50	6/50* 1.8
Lung	50	50	50	50	50	50	50	50
Alveolar/bronchiolar adenoma	11/50 B	9/50 B	5/50 B	9/50 B	5/50 B	5/50 B	2/50 B	15/50* B
Mesenteric Lymph	48	50	48	46	49	50	50	50
Congestion, NOS	7/48 1.9	7/50 2.0	14/48 1.9	10/46 1.8	15/49 1.9	20/50 2.0	18/50 2.1	29/50* 1.9
Rectum	45	49	47	46	48	47	49	46
Inflammation, Acute NOS	3/45 1/7	2/49 2.0	3/47 2.0	11/46* 2.6	3/48 2.3	0/47	1/47 3.0	15/49 2.5
Necrosis, NOS	0/45	1/49 2.0	0/47	7/46* 2.6	2/48 2.5	0/47	0/47	7/49 2.9

Organ & Disease	MALES Dose (ppm) Cont	10	50	250	FEMALES Dose (ppm) Cont	10	50	250
Ulcer, NOS	0/45	1/49 2.0	1/47 3.0	10/46* 2.6	1/48 3.0	0/47	1/47 3.0	14/49* 2.9
Small Intestine	50	50	50	50	50	50	50	50
Adenocarcinoma, NOS	0/50	0/50	0/50	9/50* M	0/50	1/50 M	0/50	4/50 M
Dilated/Distended	0/50	0/50	2/50 3.0	7/50* 2.1	2/50 2.0	0/50	11/50* 2.0	28/50* 2.0
Hyperplasia, mucosa	0/50	0/50	1/50 2.0	22/50* 2.0	1/50 4.0	0/50	0/50	19/50* 2.3

observed/# examined; mean of severity codes(1-5); B = Benign; M = Malignant; NOS = Not Otherwise Specified; *P≤0.05

Evaluation of the carcinogenicity evidence for Tribufos[1].

1. Carcinogenicity study in Crl:CD-1 (ICR)BR mice.

"Tribufos was administered in the diet to groups of 50 male and 50 female mice at 0, 10, 50 or 250 ppm for 90 weeks."

"Neoplastic lesions: The significant tumor sites were liver, lung and small intestine.

Liver: In male mice only there was a statistically significant increase in hemangiosarcoma at 250 ppm (HDT).

Lung: In female mice only there was a statistically significant increase in alveolar/bronchiolar adenoma at 250 ppm (HDT).

Small intestine: There were increases in adenocarcinoma in both sexes at 250 ppm which were statistically significant in male mice only. This tumor type is cnsidered to be rare in this strain with a reported incidence of 0/50 in each of three studies at the Registrant's racility (1980-1985)."

"Compound-related non-neoplastic effects included statistically significant decreases in brain, plasma and red blood cell cholinesterasse activity, were observed at all doses in both sexes. Increases in mortality which occured

1) Quoted from the Peer Review document.

late in the study (between weeks 72 and 90) in both sexes at 250 ppm were not considered to compromise the study findings. The Committee concluded that dosing was adequate for assessing the carcinogenic potential of Tribufos."

"The Committee classified Tribufos as a Group C (possible) human carciongen, based on the findings of tumors in both sexes at multiple sites in the mouse study. Although the tumors were later occuring, they were malignant in the male liver and in the male and female small intestine (a rare type witha a background ocurence of 0/50 in both sexes at the testing facility).

Ancillary evidence from mutagenicity studies did not indicate much concern; SAR was unavailable. However, based on the multiple and rare tumor types in 2 sexes and their malignancy, the consensus of the Committee was that a low dose extrapolation model applied to the experimantal animal tomer data should be used for puantification of human risk (Q_1*) for Tribufos."

A quantitative risk assessment of the mouse tumer incidence has been performed and the following Q_1*s calculated (Pettigrew 1993).

	Dose (ppm)				
	0	10	50	250	Q_1*
Male					
Liver Hemangiosarcoma	1/49	1/48	4/47	4/47	1.136×10^{-1}
Small Intestine Adenocarcinoma	0/47	0/48	0/47	9/47	0.479×10^{-1}
Combined	1/47	1/48	4/47	16/47	2.227×10^{-1}
Female					
Alveolar/Bronchiolar Adenoma	5/49	5/45	2/44	15/47	1.190×10^{-1}

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